I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: October 3, 2006 Signature: (Sharon M. Sinich)

Docket No.: 9189
(01017/40451B)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brockhaus et al.

Application No.: 08/444,790 Art Unit: 1646

Filed: May 19, 1995 Examiner: Z. Howard

For: HUMAN TNF RECEPTOR

AMENDMENT AND REQUEST FOR RECONSIDERATION

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This amendment is in response to the Office Action mailed April 3, 2006 (the "Action"), in which all pending claims 62, 66, 67, 102-107, 110-114 and 119-138 were rejected under 35 U.S.C. §§ 103 and 112, first paragraph. Reconsideration and withdrawal of the rejections are respectfully requested in light of the following amendment and remarks. This response is timely filed with a petition and fee for three-month extension of time.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 4 of this paper.

Remarks begin on page 10 of this paper.

AMENDMENTS TO THE SPECIFICATION

In the first line of the specification, please replace the first sentence with the following:

This is a division of application Serial Number 08/095,640, filed July 21, 1993; now U.S. Patent No. 5,610,279, which is a continuation application of Serial Number 07/580,013, filed September 10, 1990, now abandoned. This application claims priority under 35 U.S.C. § 119 to application Serial Numbers 3319/89, 746/90 and 1347/90, filed on September 12, 1989, March 8, 1990 and April 20, 1990, respectively, all in Switzerland. This application also claims priority under 35 U.S.C. § 119 to European Patent Application Number ~~99100703.0~~ 90116707.2 (now Patent Number EP ~~0939121~~ 0417563), filed August 31, 1990.

Please amend the title to read:

--HUMAN TNF RECEPTOR FUSION PROTEIN—

Please replace the paragraph starting at page 17, line 4 with the following amended paragraph:

--Suitable expression vectors include, for example, vectors such as pBC12MI [ATCC 67 109], pSV2dhfr [ATCC 37 146], pSVL [Pharmacia, Uppsala, Sweden], pRSVcat [ATCC 37 152] and pMSG [Pharmacia, Uppsala, Sweden]. The vectors "pK19" and "pN123" used in Example 9 are especially preferred vectors. These can be isolated according to known methods from E. coli strains HB101(pK19) and HB101(pN123) transformed with them [42]. These E. coli strains have been deposited on the 26th January 1990 at the Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) in Braunschweig, FRG, under DSM 5761 for HB101(pK19) and DMS 5764 for HB101(pN123). For the expression of proteins which consist of a soluble fragment of non-soluble TNF-BP and an immunoglobulin fragment, i.e. all domains except the first of the constant region of the heavy chain, there are especially suitable pSV2-derived vectors as described, for example, by German, C. in "DNA Cloning" [Vol. II., edt. by Glover, D. M., IRL Press, Oxford, 1985].

The vectors pCD4-Hμ (DSM 5315, deposited on 21st April 1989), pDC4-Hγ1 (DSM 5314, deposited on 21st April 1989) and pCD4-Hγ3 (DSM 5523, deposited on 14th September 1989) which have been deposited at the Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) in Braunschweig, FRG, and which are described in detail in European Patent Application No. 90107393.2 are especially preferred vectors. This European Patent Specification and the equivalent Applications referred to in Example 11 also contain data with respect to the further use of these vectors for the expression of chimeric proteins (see also Example 11) and for the construction of vectors for the expression of such chimeric proteins with other immunoglobulin fragments.--

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the applications:

Listing of Claims:

Claims 1-61 (canceled)

62. (currently amended) A protein comprising

(a) a human tumor necrosis factor (TNF)-binding soluble fragment of an insoluble human TNF receptor, wherein the insoluble human TNF receptor (i) specifically binds human TNF ~~tumor necrosis factor (TNF)~~, (ii) has an apparent molecular weight of about 75 kilodaltons on a non-reducing SDS-polyacrylamide gel, and (iii) comprises ~~a fragment of~~ the amino acid sequence ~~set forth in SEQ ID NO: 4~~ LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10); and

(b) all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain of said constant region;

wherein said protein specifically binds human TNF.

Claims 63-101 (canceled)

102. (currently amended) The protein of claim 62 ~~or 66~~, wherein the soluble fragment comprises the peptides LCAP (SEQ ID NO: 12) and VFCT (SEQ ID NO: 8).

103. (previously presented) The protein of claim 102, wherein the soluble fragment further comprises the peptide LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10).

104. (canceled)

105. (currently amended) The protein of claim [[104]] 62, wherein said human immunoglobulin IgG heavy chain is IgG_1.

106. (currently amended) A protein comprising

(a) a human tumor necrosis factor (TNF)-binding soluble fragment of an insoluble human TNF receptor, wherein the insoluble human TNF receptor (i) specifically binds human TNF ~~tumor necrosis factor (TNF)~~, (ii) has an apparent molecular weight of about 75 kilodaltons on a non-reducing SDS-polyacrylamide gel, and (iii) comprises ~~a fragment of~~ the amino acid sequences ~~set forth in SEQ ID NO: 4~~ LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10), LCAP (SEQ ID NO: 12), VFCT (SEQ ID NO: 8), NQPQAPGVEASGAGEA (SEQ ID NO: 9) and VPHLPAD (SEQ ID NO: 13),

wherein the soluble fragment comprises the peptides LCAP (SEQ ID NO: 12) and VFCT (SEQ ID NO: 8); and

(b) all of the domains of the constant region of a human IgG_1 heavy chain other than the first domain of the constant region;

wherein said protein specifically binds human TNF.

107. (currently amended) A recombinant protein encoded by a polynucleotide which comprises two nucleic acid subsequences,

(a) one of said subsequences encoding a human TNF-binding soluble fragment of an insoluble human TNF receptor protein having an apparent molecular weight of about 75 kilodaltons on a non-reducing SDS-polyacrylamide gel, said soluble fragment comprising ~~a fragment of~~ the amino acid sequence ~~of SEQ ID NO: 4~~ LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10), and

(b) the other of said subsequences encoding all of the domains of the constant region of the heavy chain of a human IgG immunoglobulin other than the first domain of said constant region,

wherein said recombinant protein specifically binds human TNF.

Claims 108 and 109 (canceled)

110. (previously presented) The protein of claim 107, wherein the soluble fragment comprises the peptides LCAP (SEQ ID NO: 12) and VFCT (SEQ ID NO: 8).

111. (previously presented) The protein of claim 110, wherein the soluble fragment further comprises the peptide LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10).

112. (canceled)

113. (currently amended) The protein of any one of claims 107, 110 or 111, wherein said human immunoglobulin heavy chain is IgG_1.

114. (currently amended) A pharmaceutical composition comprising the recombinant protein of any of claims 62, [[66,]] 107, 134 or 135 and a pharmaceutically acceptable carrier material.

Claims 115-118. (canceled)

119. (previously presented) The protein of claim 62, wherein the protein is purified.

120. (previously presented) The protein of claim 62, wherein the protein is produced by CHO cells.

121. (currently amended) The protein of claim 62, wherein the protein consists of (a) the soluble fragment of the receptor and (b) all of the domains of the constant region of the human immunoglobulin IgG heavy chain other than the first domain of the constant region.

122. (canceled)

123. (currently amended) The protein of claim [[104]] 62, wherein said domains of the constant region of the human immunoglobulin heavy chain consist essentially of the immunoglobulin amino acid sequence encoded by pCD4Hγ1 vector (deposited at Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) in Braunschweig, FRG

under No. DSM 5314) or by pCD4-Hγ3 vector (deposited at Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) in Braunschweig, FRG under No. DSM 5523).

124. (previously presented) The protein of claim 105, wherein said domains of the constant region of the human immunoglobulin heavy chain consist essentially of the immunoglobulin amino acid sequence encoded by pCD4Hγ1 vector (deposited at Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) in Braunschweig, FRG under No. DSM 5314).

125. (previously presented) The protein of claim 106, wherein the protein is purified.

126. (previously presented) The protein of claim 106, wherein the protein is produced by CHO cells.

127. (previously presented) The protein of claim 106, wherein the protein consists of (a) the soluble fragment of the receptor and (b) all of the domains of the constant region of the human IgG_1 heavy chain other than the first domain of the constant region.

128. (previously presented) The protein of claim 106, wherein the soluble fragment further comprises the peptide LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10).

129. (previously presented) The recombinant protein of claim 107, wherein the recombinant protein is purified.

130. (previously presented) The recombinant protein of claim 107, wherein the recombinant protein is produced by CHO cells.

131. (previously presented) The recombinant protein of claim 107, wherein the protein consists of (a) the soluble fragment of the receptor and (b) all of the domains of the constant region of the human IgG_1 heavy chain other than the first domain of the constant region.

132. (currently amended) The protein of claim [[112]]]] 107, wherein said domains of the constant region of the human immunoglobulin heavy chain consist essentially of the immunoglobulin amino acid sequence encoded by pCD4Hγ1 vector (deposited at Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) in Braunschweig, FRG under No. DSM 5314) or by pCD4-Hγ3 vector (deposited at Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) in Braunschweig, FRG under No. DSM 5523).

133. (previously presented) The protein of claim 113, wherein said domains of the constant region of the human immunoglobulin heavy chain consist essentially of the immunoglobulin amino acid sequence encoded by the DNA insert of pCD4Hγ1 vector (deposited at Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) in Braunschweig, FRG under No. DSM 5314).

134. (currently amended) A protein consisting of

(a) a human tumor necrosis factor (TNF)-binding soluble fragment of an insoluble human TNF receptor, wherein the insoluble human TNF receptor (i) specifically binds human TNF, and (ii) has an apparent molecular weight of about 75 kilodaltons on a non-reducing SDS-polyacrylamide gel and (iii) comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10),

wherein the soluble fragment comprises the peptides LCAP (SEQ ID NO:12) and VFCT (SEQ ID NO:8), and

(b) all of the domains of the constant region of a human IgG_1 heavy chain other than the first domain of the constant region,

wherein the protein specifically binds human TNF, and

wherein the protein is produced by CHO cells.

135. (previously presented) The protein of claim 134, wherein the soluble fragment comprises the peptide LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10).

136. (previously presented) The protein of claim 134, wherein the protein is purified.

137. (previously presented) A pharmaceutical composition comprising the recombinant protein of claim 105 and a pharmaceutically acceptable carrier material.

138. (canceled)

139. (new) A method of binding human TNF *in vivo* comprising the step of administering to a subject the pharmaceutical composition of claim 137.

140. (new) A protein comprising

(a) a human tumor necrosis factor (TNF) binding soluble fragment of the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC on _____ under accession number _____ ; and

(b) all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain of said constant region;

wherein said protein specifically binds human TNF.

141. (new) The protein of claim 140 consisting of the soluble fragment and all the domains of the constant region of the human immunoglobulin IgG heavy chain other than the first domain of said constant region.

142. (new) The protein of claim 140

wherein the protein is expressed by a mammalian host cell.

143. (new) The protein of claim 142, wherein the mammalian host cell is a CHO cell.

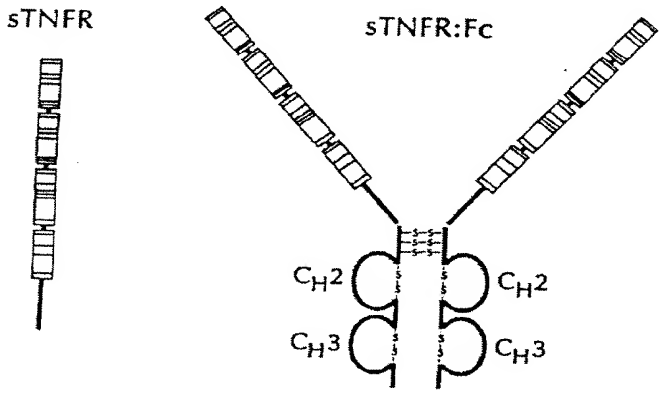
144. (new) The protein of claim 142 consisting of the soluble fragment and all the domains of the constant region of the human immunoglobulin IgG heavy chain other than the first domain of said constant region.

REMARKS

I. Preliminary Remarks

Claims 62, 102-103, 104-107, 110-111, 113-114, 119-137 and 139 as amended herein are pending. Applicants thank Examiners Howard, Nickolls and Kemmerer for the courtesy of the interview kindly granted on June 22, 2006 to inventor Dr. Werner Lesslauer and Applicant's attorneys Li-Hsien-Rin-Laures, Sharon Sintich and Rosemary Sweeney. During the interview, Applicants discussed the outstanding rejections, the data described herein and the claim amendments presented herein.

During the interview, Applicants discussed the trimeric nature of tumor necrosis factor (TNF) alpha and the homodimeric nature of the claimed fusion proteins, which comprise soluble fragments of p75 tumor necrosis factor receptor (TNFR) fused to all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain (CH1) of said constant region. The immunoglobulin portion of the claimed fusion protein, which includes the hinge, second domain (CH2), and third domain (CH3) of the heavy chain constant region, naturally homodimerizes through cysteine bonding between the two hinge regions. See, e.g., Figure 1 on page 1550 of Mohler et al., J. Immunol., 151:1548-1561 (1993) ("Mohler", Exhibit C to Applicants' response mailed January 12, 2005), which is reproduced below:



The cysteine-bonding between the hinge regions also occurs in intact natural immunoglobulins. For example, IgG antibody (which include two heavy and two light

chains) contains two heavy chain constant regions that are dimerized through cysteine-bonding. Other immunoglobulin classes, such as IgM and IgA, multimerize even further. Sell, Immunology, Immunopathology and Immunity, 4th Edition, Elsevier Science Publishing Co., New York, 1987, at pp. 85-91 (Exhibit B, hereto). Applicants have amended the claims to recite IgG to more clearly and distinctly point out the homodimeric nature of the claimed fusion proteins.

The dimeric nature of the claimed TNF-binding fusion proteins and the hypothesized binding interaction of one exemplary embodiment with a TNF trimer is illustrated in the figure attached hereto as Exhibit A. As Applicants noted during the interview, this figure is not based on crystal structure data but rather on theoretical molecular modeling. For comparison purposes, the figure also includes a molecular model of an antibody, which contains two heavy chains and two light chains, as well as the hypothesized binding of this antibody to TNF trimers.

II. Information Disclosure Statement

During the interview, Applicants clarified with Examiner Howard the meaning of the statement in the Interview Summary mailed May 16, 2006 that the Examiner "agrees to consider the material presented as Exhibit A-M." Examiner Howard indicated that he would consider not only the exhibits attached to the Supplemental Information Disclosure Statement submitted on December 20, 2005 but also the statements in the Information Disclosure Statement itself.

As noted in the Supplemental Information Disclosure Statement submitted on December 20, 2005, the file history of U.S. App. No. 08/478,995 may be relevant to the instant application, including the "Request Under 37 C.F.R. § 1.607 for Interference with U.S. Patent 5,610,279 to Brockhaus et al." filed on October 6, 2000.

III. The Outstanding Objections and Rejections

In response to the Examiner's objections to the specification, the specification has been amended to update the status of priority applications in the first sentence and correct

a typographical error. The title has been amended to be more descriptive of the fusion proteins presently claimed.

In the Action, all of the previous rejections were withdrawn and new rejections were instituted. Claims 123, 124, 132 and 133 were rejected under 35 U.S.C. § 112, first paragraph, as assertedly lacking enablement because assurances as to public availability of the referenced deposits and insertion of the date of deposit were required. In response, Applicants have amended the specification to include the respective date of deposits and are supplying herewith a Budapest Treaty declaration in compliance with 37 C.F.R. § 1.808.

Claims 62, 66, 67, 102-107, 110-114, 119-122, 125-131 and 134-138 were rejected under 35 U.S.C. § 103 (a) as allegedly unpatentable over Dembic *et al,* Cytokine 2: 231-237, 1990 ("Dembic") in view of Capon *et al.* Patent No. 5,116,964 ("Capon"). In addition, all pending claims 62, 66, 67, 102-107, 110-114 and 119-138 were rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. These last two rejections are addressed in turn below.

IV. The Rejection Under 35 U.S.C. § 103 Should be Withdrawn

The claims were rejected as obvious over Dembic in view of Capon. The Action states at page 11 that Dembic teaches the full length amino acid sequence of p75 TNFR and the extracellular domain that forms a TNF-binding soluble fragment. Capon was cited for teaching a fusion of truncated murine lymphocyte homing receptor (MHLR) to the Fc region of human IgG_1 just upstream of the hinge domain. The Examiner acknowledged at page 11 of the Action that Dembic does not teach fusion of soluble TNFR with any portion of an immunoglobulin heavy chain constant region. Similarly, Capon does not disclose TNFR as a candidate for fusion with an immunoglobulin fragment.

However, the Action states on page 12 that it would have been obvious to fuse the extracellular portion of the TNFR sequence taught by Dembic to the fragment of human IgG_1 taught by Capon, for use in affinity purification of the TNF ligand. The Action further

states that Capon teaches production of such hybrid immunoglobulins in CHO cells, purification of the resulting fusion protein, and sterile isotonic formulations containing such fusion proteins that would be encompassed by claims to "pharmaceutical compositions."

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2142. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). To reach a proper determination under 35 U.S.C. §103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person.

As discussed in further detail below, Applicants respectfully submit that the cited art teaches away from combining Dembic with Capon, and that there was no reasonable expectation of success in producing the claimed TNF-binding fusion proteins because of the uncertainties associated with the trimeric structure of TNF and the unknown spatial geometry of the binding interaction between TNF and TNFR. Thus, there is no *prima facie* case of obviousness. Moreover, as noted during the interview, there are a multitude of unexpected results that render Applicants' claimed TNF-binding fusion proteins nonobvious.

A. Lack of motivation to combine Dembic and Capon

Capon teaches a vast array of possible hybrid immunoglobulins, including monomeric and homo- or hetero-multimeric forms, among which Capon specifically mentions dimeric, trimeric, and tetrameric forms. See, *e.g.*, col. 10, lines 28-30 and col. 13, lines 21-22 and 54. The motivation for fusing TNFR soluble fragments to immunoglobulin

fragments stated in the Office Action, *i.e.* for the purposes of affinity purification, does ***not*** motivate the construction of homodimeric fusion proteins such as those claimed. One of ordinary skill in the art might well have preferred a monomeric form of a TNFR-CH_2CH_3 fusion fusion for this stated purpose, because one would have expected a monomeric form to bind TNF, with much less uncertainty of success (for the reasons discussed in section B below). Thus, contrary to the conclusion drawn in the Office Action, the ordinary skilled person lacked motivation to select dimeric forms over monomeric or other forms. Moreover, Applicants dispute the assumption that there was a need for the hybrid immunoglobulins of Capon to affinity purify TNF ligand, since affinity purification of TNF was already easily carried out with anti-TNF antibody (see, *e.g.*, Bringman, Hybridoma, 6(5):489-507 (1987), attached as Exhibit D hereto, which describes production and use of anti-TNF monoclonal antibodies as immunoadsorbents to purify recombinant TNF-alpha and TNF-beta from *E. coli* lysates).

Applicants also specifically disagree that the stated motivation would extend to the making of a pharmaceutical composition, because sterile isotonic solutions, commonly used in pharmaceutical compositions, are not needed (and not normally used) in affinity purification procedures. The ordinary skilled worker would therefore not have formulated the hybrid immunoglobulins of Capon in sterile isotonic solutions if their use was as a reagent in affinity purification.

In fact, as Dr. Lesslauer explained during the interview, the cited art Capon ***teaches away*** from the construction of Applicants' claimed fusion proteins. One of ordinary skill in the art would ***not*** have fused a ***pro***-inflammatory fragment of an immunoglobulin constant region to an ***anti***-inflammatory agent such as soluble TNFR. Such pro-inflammatory or anti-inflammatory effects of the components of the fusion protein are highly relevant in the context of ***in vivo administration***, which is the main focus of Capon. See, *e.g.*, Capon at col. 1, lines 8-11, col. 4, lines 38-42, and col. 5, lines 13-20 (multiple references that object of invention is to increase *in vivo* plasma half-life).

The immunoglobulin heavy chain constant region, particularly the hinge, CH2 and CH3 domains, was known at the time of filing to be important in eliciting the pro-

inflammatory effector functions of immunoglobulins, including the initiation of both complement activation and antibody-dependent cellular cytotoxicity (ADCC). The initiating event of the complement cascade involves binding of a plasma protein called C1q to the CH2 domain of an IgG or IgM antibody. Complement activation upon C1q binding to IgG or IgM antibodies produces and regulates inflammation, leads to phagocytosis of foreign materials, and mediate direct lysis of various cells and microorganisms. Fundamental Immunology, 2nd Edition, Paul, ed., Raven Press, New York, 1989, at pp. 679-701 (Exhibit E hereto). ADCC can be initiated through binding of Fcγ receptors on the surface of cytolytic T lymphocytes, macrophages, monocytes, or NK cells to the CH2 region within the Fc portion of IgG. ADCC causes release of cytotoxic effector molecules that can that can cause prompt, nonspecific cell lysis and/or protracted but selective lysis. Paul, at pp. 735-764. (Exhibit F hereto).

Statements in Capon are consistent with this knowledge in the art that the hinge, CH2 and CH3 domains are responsible for immunoglobulin effector functions. Moreover, Capon teaches that such effector functions were expected to be retained when immunoglobulin fragments were fused to ligand binding partners. See, e.g., Capon at col. 4, lines 43-47 which states that a further object of the invention is to combine the characteristics of a ligand binding partner with immunoglobulin effector functions such as complement binding and the like, as well as Capon at col. 15, lines 7-8 (C-terminal Fc portion of an antibody contains the effector functions of IgG1). Thus, as of the effective filing date of the present application, one of ordinary skill in the art would have expected the immunoglobulin heavy chain constant region to be pro-inflammatory, even when fused to another protein.

It was believed in the art at the time that TNF (both alpha and beta) mediated a wide range of immunological responses, inflammatory reactions, and anti-tumor effects. See the first sentence of the abstract of Smith et al., *Science,* 248:1019-1023, (1990) ("Smith 1990"), Exhibit G hereto. Soluble forms of TNFR were thought to be potentially valuable for TNF inhibition, and therefore to have an anti-inflammatory effect. See Smith 1990 at page 1022, bottom of 2nd col. Thus, as of the effective filing date of the present application, one of

ordinary skill in the art would have expected a soluble fragment of TNFR to be anti-inflammatory.

One of ordinary skill in the art would not have fused a proposed anti-inflammatory agent, a soluble fragment of TNFR, to a molecule expected to enhance inflammation. Thus, Capon's teaching that their disclosed hybrid immunoglobulins retain the pro-inflammatory effector functions of the heavy chain constant region teaches away from fusing a pro-inflammatory fragment of this constant region to soluble TNFR. It was therefore not obvious to make Applicants' claimed TNF-binding fusion proteins, which the specification contemplates to be useful as anti-inflammatory agents for treating illnesses in which TNF is involved, such as immune response and inflammation. See page 11, lines 24-32 and page 12, lines 17-21 of the specification.

Thus, there was no motivation to combine Dembic and Capon for the variety of reasons discussed above, including Capon's teaching away from the combination. Without a proper combination of references, the *prima facie* case for obviousness fails.

B. No reasonable expectation of success

TNF was known to be trimeric prior to Applicants' filing date, and the biologically active form was believed to be trimeric as well. See Wingfield et al., FEBS Lett. 211: 179-84 (1987), and Smith and Baglioni, JBC 262:6951-4 (1987) (Exhibits H and I, respectively). However, the location of the receptor-binding sites on the TNF trimer was unknown, as was the exact three-dimensional structure of the TNF receptor itself and how the receptor would interact with the TNF trimer.

One of ordinary skill in the art would not have had a reasonable expectation that the claimed dimeric TNFR fusion proteins would retain TNF-binding activity. As described by Dr. Lesslauer at the interview and in his previously submitted declaration, there was uncertainty that the spatial configuration of the dimeric fusion protein would allow it to bind a trimeric ligand. The steric distances between the two TNF-binding sites in the dimer and the degree of flexibility required to accommodate the TNF trimer were unknown.

Moreover, there was uncertainty that the TNFR portion of the fusion protein would retain the three-dimensional structure of its TNF-binding site when fused to a relatively large immunoglobulin heavy chain fragment, especially after recombinant production in a host cell.

The Declaration under 37 C.F.R. § 1.132 of Dr. Werner Lesslauer (denoted as "Lesslauer Declaration [III]" and attached as Exhibit B to Applicants' response mailed January 12, 2005) states that: "the spatial geometry of the receptor-binding site was unknown. It would have been entirely possible for the fusion with IgG fragments to have created a spatial configuration which might well have contained TNF receptor sequences but which, because of its spatial structure, was not able to bind TNF alpha at all."

Thus, at the time of Applicants' effective filing date, there was no reasonable expectation of success in producing the claimed TNF-binding p75 TNFR fusion proteins, and the Examiner's *prima facie* case of obviousness fails.

C. Unexpected results

During the interview, Applicants discussed and the Examiners agreed to consider data showing a number of unexpected results associated with the claimed TNF-binding fusion proteins. Unexpectedly superior properties, unexpectedly different properties, and the absence of expected properties are all relevant factors that can rebut a prima facie case of obviousness. According to MPEP Section 716.02(a), "[a] greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a prima facie case of obviousness." *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). The absence of a property which a claimed invention would have been expected to possess based on the teachings of the prior art is also evidence of unobviousness. *See Ex parte Mead Johnson & Co.* 227 USPQ 78 (Bd. Pat. App. & Inter. 1985).

The first category of unexpected results relates to the unique binding stoichiometry of the claimed dimeric TNF-binding fusion proteins with trimeric TNF, and the corresponding lack of ability to form aggregated protein complexes. The data presented at the interview indicated that, under the conditions tested, a homodimeric fusion of the extracellular domain of p75 TNFR to the hinge region of IgG1 (denoted as "etanercept") bound ***only one*** TNF trimer, not two TNF trimers, as would be expected from the dimeric nature of the TNFR fusion. It is, thus, possible that the two TNFR "arms" of the fusion protein each bind one TNF molecule within the TNF trimer, thus binding two out of the three TNFs in a trimer. See the illustrative molecular model in Exhibit A. Data was also presented that showed the ***absence*** of an expected property in etanercept, *i.e.* the absence of the ability to form aggregated protein complexes when combined with TNF trimers. See, e.g., Kohno et al., Presentation 1495, poster 271, presented at the American College of Rheumatology Annual Meeting, November 13-17, 2005, San Diego, CA ("Kohno 2005", attached as Exhibit L hereto).

The second category of unexpected results relates to the surprising reduction in inflammatory immunoglobulin effector functions of the claimed fusion proteins. Data was presented to show that, unlike immunoglobulins which also contain the hinge-CH2-CH3 region responsible for effector function, etanercept ***did not bind*** FcγR and C1q under the conditions tested. As a result, etanercept exhibited ***little or no*** antibody-dependent cellular cytotoxicity (ADCC) and a ***marked reduction*** in complement-dependent cytotoxicity (CDC), properties that were unexpected for a fusion molecule containing the CH2 and CH3 regions. See, e.g., Khare et al, Poster 715 presented at the Annual Meeting of the Society for Investigative Dermatology (SID), May 3-5, 2006, Philadelphia, PA ("Khare 2006", attached as Exhibit R hereto) and Kohno (2005).

The third category of unexpected results relates to the improved binding kinetics (both affinity and kinetic stability) and potency in *in vitro* biological activity assays. Applicants previously presented data for two different dimeric soluble p75 TNFR fusions, one of the IgG1 subtype and another of the IgG3 subtype. See the Declaration under 37 C.F.R. § 1.132 of Dr. Werner Lesslauer (denoted as "Lesslauer Declaration [III]" and

attached as Exhibit B to Applicants' response mailed January 12, 2005). The relatively increased binding affinity of both dimeric products compared to a monomeric soluble fragment of p75 TNFR was unexpected, particularly in view of the uncertainty that the dimeric product would even bind TNF at all. The even more marked ***1000-fold*** increase in the *in vitro* biological activity of the dimeric product, as measured in an L929 cytolysis assay, is quite surprising. See Mohler et al. (1993), J. Immunol. 151: 1548-61 (Exhibit C to Applicants' January 12, 2005 response).

The expectations in the art and the evidence supporting the surprising properties of the claimed TNF-binding fusion proteins is discussed in further detail below.

1. Lack of aggregation ability

As discussed during the interview, the claimed TNF-binding fusion proteins unexpectedly lack the ability to form large aggregated protein complexes when binding TNF. The absence of this ability to aggregate is surprising because it had long been expected in the art that linking two ligand binding partners to create a dimeric binding molecule would result in the ability to bind two ligands, allowing formation of aggregated complexes and precipitation.

As a general example of a bivalent binding compound, Larsson and Mosbach, FEBS Lett. 98(2):333-338 (1979) ("Larsson", Exhibit J hereto) shows that a bifunctional NAD compound prepared by covalently linking two NAD compounds (denoted Bis-NAD) was able to complex with and precipitate the tetrameric enzyme lactate dehydrogenase. Irwin and Tipton, Chapter 22, "Affinity Precipitation Methods" in Methods in Mol. Bio., 59:217 (1996) ("Irwin", Exhibit K hereto) refers to this as the "bis-ligand" or "functional ligand" approach using "two identical ligands connected by a spacer arm. If the spacer is long enough, each ligand can bind to a ligand binding site on a different protein molecule."

Capon confirms that this general expectation that dimeric binding molecules can bind more than one ligand would be expected to apply to the hybrid immunoglobulins disclosed in Capon. See Capon at col. 4, lines 52-56, which states that the invention provides

"multifunctional molecules in which a plurality of ligand binding partners (each of which may be the same or different) are assembled, whereby the molecules become capable of binding and/or activating more than one ligand."

One technique for detecting the formation of aggregates or complexes is the classic Ouchterlony (double diffusion) test, typically used to detect aggregation of antibodies and antigens. For example, the ligand is placed in the center well of an agarose gel and the ligand binding partner(s) or controls are placed in peripheral wells that are equidistant from the center well. As the ligand and ligand binding partner diffuse towards each other through the gel, they bind and aggregate, causing visible precipitation lines to form in the agarose gel. Results of an Ouchterlony test for bis-NAD and its ligand LDH are shown in Figure 3 at page 337 of Larsson (Exhibit J), where precipitation lines can be seen for peripheral wells 1-3 (containing bis-NAD) but not for wells 4-6 (containing monomeric NAD or buffer only). Thus, the dimeric products form aggregates while the monomeric product does not.

In contrast, Applicants presented data during the interview that demonstrate that the claimed TNFR fusion proteins do ***not*** form large aggregated complexes with TNF. See Kohno 2005 (Exhibit L). Figure 6 of Kohno 2005 displays results of an Ouchterlony test for three different TNF-binding compounds, a soluble p75 TNFR/Ig fusion (etanercept), and two anti-TNF antibodies adalimumab and infliximab. In the control experiment (Figure 6A), the center well was filled with a goat anti-Fc antibody which would bind to the common Fc portion of all three TNF-binding compounds. As expected, precipitation lines are formed for all three wells (etanercept, adalimumab and infliximab). In the test experiment (Figure 6B), the center well was filled with TNF. It can be seen that precipitation lines formed for the anti-TNF antibodies (adalimumab and infliximab) but ***not*** for etanercept, indicating that no TNF-etanercept aggregates were detected.

This lack of ability to aggregate is likely due to the unique binding stoichiometry of etanercept with TNF trimers. When etanercept and TNF are mixed at varying molar ratios under the experimental conditions used, size-exclusion chromatography and subsequent determinations of molecular mass and radius by a light scattering detector (SEC-LS) show that etanercept will bind ***only one*** TNF trimer. See Figures 2 and 5 of Kohno

2005. (Exhibit L). When etanercept is present in excess, two molecules of etanercept will bind one TNF trimer (the 300kD complex of Figure 6). However, complexes were not observed in which one molecule of etanercept bound two TNF trimers.

The lack of aggregation ability is an unexpected result and is advantageous in conditions where inflammation is undesirable. For example, physical proximity of IgG molecules, such as occurs in aggregated complexes, plays an important role in complement activation. Fundamental Immunology, *supra,* at p. 681. Further, deposition of antigen:antibody aggregates (also called immune complexes or antigen-antibody complexes) in tissue sites was well recognized to be pathogenic. Type III hypersensitivity reactions, serum sickness and autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis were believed to be the result of such immune complexes. Immunology, 1st Edition, Klein ed., Blackwell Scientific Publications, Cambridge, MA 1990 at pp. 446-447 (attached as Exhibit M hereto).

Thus, against the expectation in the art as of the application's effective filing date that dimeric TNFR fusion proteins would bind two ligands and form aggregates, the observed binding stoichiometry and lack of ability to aggregate is an unexpected advantageous property that renders the claimed TNF-binding fusion proteins nonobvious.

2. Markedly reduced immunoglobulin effector function

The claimed TNF-binding fusion proteins also exhibit a surprising reduction in pro-inflammatory immunoglobulin effector functions. As discussed above in section A, Capon teaches that its hybrid immunoglobulin fusion proteins were expected to retain immunoglobulin effector functions, which were known to include activities such as complement binding and activation and antibody-dependent cellular cytotoxicity (ADCC). Capon's teaching is confirmed by data reported for other immunoglobulin fusions such as CD4/IgG fusions, which showed that such fusions retained both complement binding activity and ADCC.

For example, Byrn et al., Nature, 344:667-670 (April 1990) ("Byrn", Exhibit N hereto) reported that CD4/IgG fusion mediated ADCC towards HIV-infected cells. Byrn at page 668, first col. states that "CD4 immunoadhesin mediates ADCC towards HIV-infected [cells] in a dose-dependent manner (Fig. 2*a* and *b*). Soluble recombinant (rCD4) does not mediate ADCC (not shown), but can inhibit cell lysis mediated by CD4 immunoadhesin. . . ." The corresponding data are shown in Figure 2 of Byrn (Fig. 2a, lanes a-d show the dose-dependent ADCC as measured by percent cell lysis; lanes e-f show inhibition by soluble rCD4).

Traunecker et al., Nature 339:68-70, 1989 ("Traunecker", Exhibit O hereto) reported that a CD4/IgG fusion, wherein soluble CD4 was fused to the hinge region of an immunoglobulin heavy chain, retained immunoglobulin effector functions as measured by ability to bind complement protein C1q and the receptor that initiates ADCC (Fcγ receptor). Traunecker states at page 69, 1st-2nd col. that: "the effector functions of normal immunoglobulin molecules, such as binding to Fcγ receptors and C1q were kept intact in the hybrid molecules (Fig. 3). This suggests that removal of the CH1 domain does not create major structural alterations in the regions of the CH2 domain responsible for C1q and Fcγ receptor binding." See the data displayed in Figures 3a, 3b and 3c at page 69 of Traunecker. Capon, Nature, 337:525-531 (1989) ("Capon 1989", Exhibit P hereto) at page 528, bottom left col., similarly states that their CD4/Ig fusion bound well to FcγR receptor. Although Capon 1989 stated that their CD4/Ig fusion did not bind C1q, the article states that this result was "surprising" (page 529, bottom left col.), indicating that the authors expected to see the results described in Traunecker.

In contrast, Applicants presented during the interview published data showing that the claimed TNFR fusion proteins do not appear to bind FcγR or C1q, and exhibit markedly reduced antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) as measured by in vitro assays. See Khare 2006 (Exhibit R).

Figures 8 and 9 of Kohno (2005) (Exhibit L) display data from experiments evaluating whether etanercept can bind FcγR and C1q in the presence of TNF. To investigate binding to FcγRI and FcγRII, a cell line expressing FcγRI and FcγRII was incubated with

radiolabeled etanercept, infliximab, or adalimumab in the presence of an 0.8-fold molar excess of TNF, a 200-fold excess of Fc, or a 200-fold excess of unlabeled etanercept, infliximab, or adalimumab. Infliximab and adalimumab are both anti-TNFα antibodies. Binding to C1q was tested by binding C1q to a microtiter plate via an anti-C1q antibody and then adding to the wells either etanercept, infliximab, or adalimumab plus the same competitors used in the FcγR binding experiment. In both experiments, unbound etanercept or anti-TNFα antibody was washed away, and the amount of bound labeled etanercept or antibody was quantitated with a gamma counter. The results show that etanercept did not bind specifically to C1q, whereas each of the antibodies did in the presence of TNF. Figure 9. Similarly, both antibodies showed substantially enhanced binding to cells expressing FcγRI and FcγRII and to C1q in the presence of TNF, whereas etanercept did not. See Figures 8 and 9.

Barone et al., Arthritis Rheum., v42(9) supplement, September 1999 (S90) ("Barone", Exhibit Q hereto) reported that etanercept was unable to mediate CDC. Barone states that "infliximab was able to mediate complement-dependent killing of the TNF-expressing cells (60% lysis at 0.5 mg/mL). In contrast, etanercept was not able to mediate complement-dependent killing of the TNF-expressing cells (0% lysis at 1.0 mg/mL)."

Figures 3 and 4 of Khare 2006 (Exhibit R) also demonstrate that etanercept produces little or no ADCC and significantly lower CDC compared to antibodies which contain an analogous hinge-CH2-CH3 region. In the assays described, MT-3 cells, which express membrane-bound TNF, were incubated with varying concentrations of etanercept or infliximab. For the ADCC assay, the cells were then incubated with purified human peripheral blood mononuclear cells at a 10:1 or 40:1 ratio, while for the CDC assay, the cells were incubated with human complement-rich serum (or complement-depleted serum as a negative control). Propidium iodide, a dye which binds to dead or dying cells, was added and the degree of resulting cell death was measured. The results show that although infliximab tested in the same assay was able to mediate ADCC in a dose-dependent manner, etanercept mediated ***little or no detectable*** ADCC. See Figure 3 of Khare 2006. Similarly, etanercept exhibited ***markedly less*** CDC compared to infliximab. See Figure 4 of Khare 2006.

Thus, against the expectation in the art as of the application's effective filing date that the claimed TNFR fusion proteins would bind to FcγR or C1q and retain pro-inflammatory immunoglobulin effector functions, the observations that a fusion of soluble p75 TNFR to the hinge region of IgG ***lacks*** ability to bind FcγR or C1q and exhibits ***markedly*** decreased ADCC and CDC effects are quite surprising unexpected and advantageous results that show that the claimed invention was unobvious.

3. Binding affinity, kinetic stability and potency

As discussed in Applicants' previous response, the claimed TNF-binding fusion proteins also exhibit unexpectedly advantageous properties in terms of binding kinetics (both affinity and kinetic stability) and potency in *in vitro* biological activity assays. Applicants previously provided a Declaration under 37 C.F.R. § 1.132 of Dr. Werner Lesslauer (denoted as "Lesslauer Declaration [III]" and attached as Exhibit B to Applicants' response mailed January 12, 2005) that discusses these unexpected results. Lesslauer Declaration [III] presents data showing that a fusion of soluble p75 TNFR to the hinge region of IgG3 exhibit (a) surprisingly good binding affinity, (b) unexpectedly higher kinetic stability, and (c) superior inhibition of TNF biological activity. Data reported by another group of scientists in the Mohler article (Exhibit C to Applicants' January 12, 2005 response) shows that a fusion of soluble p75 TNFR to the hinge region of IgG1, a different IgG subtype, also exhibits unexpectedly increased binding affinity and even more surprisingly increased biological activity *in vitro*.

Lesslauer Declaration [III] provides experimental evidence demonstrating unexpectedly superior activity of a recombinant fusion protein comprising the extracellular domain of the 75 kD TNF receptor (also known as p75 TNFR, p80 TNFR, or TNFR-II) fused to the hinge region of IgG3 (denoted as "p75sTNFR/IgG" in the Declaration), compared to the soluble TNFR fragment alone. See paragraph 4 of the Declaration. Lesslauer declaration [III] states: "Surprisingly, however, the fusion construct obtained even had an excellent binding activity. In addition, an unexpectedly higher kinetic stability and a surprisingly improved inhibition of the effect of TNFα in biological cell culture tests were discovered as well."

Experiment I of Lesslauer Declaration [III] is a binding study that measured dissociation of the test TNF binding protein from radiolabeled TNFα in the presence of unlabeled TNFα. Dissociation of the dimeric p75sTNFR/IgG fusion was compared to dissociation of the monomeric p75sTNFR. As shown in the figure, at the six-minute time point, essentially all of the TNFα had dissociated from the monomeric p75sTNFR, while only about half of the TNFα had dissociated from the dimeric p75sTNFR/IgG fusion, which indicates that the dimeric product binds for a longer period of time and has a higher kinetic stability than the monomeric product. Experiment II of Lesslauer Declaration [III] shows that the same dimeric product (at about half the molar concentration of the monomeric product) also produced superior inhibition of TNF biological activity *in vitro*, in an assay measuring TNF-induced proliferation of mononuclear cells.

Mohler (Exhibit C to Applicants' January 12, 2005 response) provides further experimental evidence demonstrating unexpectedly superior activity of a recombinant fusion protein comprising the extracellular domain of the 75 kD TNF receptor (referred to in Mohler as p80) fused to the hinge region of IgG1 (denoted as "sTNFR:Fc" in the article). See Mohler page 1554, col. 2 bottom. As Applicants discussed during the interview, Mohler shows that the dimeric sTNFR:Fc had about 50 fold higher binding affinity for TNF than the monomeric soluble TNFR fragment denoted as "sTNFR" (page 1550, col. 2 and Fig. 2A). Mohler also shows that the dimeric sTNFR:Fc was about 1000 fold more effective in neutralizing TNF-induced cytotoxicity in L929 cells (page 1551, col. 1 and Fig. 2B) than the monomeric sTNFR. This 3-log increase in *in vitro* biological activity was unexpected in magnitude and was even higher than could have been predicted on the basis of the already unexpectedly increased binding affinity.

In contrast, no such increase in affinity and potency was observed for prior art immunoglobulin fragment fusions such as CD4-IgG fusion. For example, Capon, Nature, 337:525-531 (1989) ("Capon 1989", Exhibit P hereto) at p. 526, bottom right col., states "The dissociation constant (Kd) for the interaction of each immunoadhesin with gp120, calculated by Scatchard analysis (Fig. 3a, inset), was indistinguishable from that of soluble rCD4."

Capon 1989 in Fig. 5 and at p. 529, bottom right col., also states "Both CD4 immunoadhesins blocked cell killing with the same potency as soluble rCD4."

In view of the uncertainty that the claimed dimeric TNF-binding fusion proteins would even retain TNF-binding activity, discussed above in section B, the observed increased binding affinity, increased kinetic stability, and 1000-fold increase in *in vitro* biological activity are unexpected and advantageous results that show that the claimed invention was unobvious.

V. The Rejection Under 35 U.S.C. § 112 Should be Withdrawn

The claims were also rejected for asserted lack of written description. It was the Examiner's position that, because SEQ ID NO: 4 is missing 48 N-terminal amino acids of TNFR that are allegedly necessary for TNF-binding, Applicants do not disclose any amino acid sequence that can actually bind TNF. Pages 7-8 of the Action. However, as discussed during the interview, the specification does disclose the full length amino acid sequence of TNFR and TNF-binding deletion fragments thereof by citing Smith, et al., Science 248:1019-1023 (1990) ("Smith 1990", Exhibit G hereto). See page 10, lines 9-10 of the specification. Smith 1990 discloses the full length p75 TNFR nucleotide and amino acid sequence in Figure 3.

The Office Action also asserted that the specification fails to provide a sufficient representative number of species, or alternatively sufficient identifying characteristics, to support the claimed genus of soluble fragments of TNF fused to all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than CH1. Page 8 of the Action. Applicants respectfully disagree. There is sufficient evidence to show that Applicants were in possession of a representative number of species to support the claimed genus, through a disclosure of relevant, identifying characteristics, i.e., a variety of TNFR fragments with TNF-binding activity, and the functional characteristic of TNF-binding coupled with a known correlation between this function and the sequence structure. See MPEP §2163.

Smith 1990 discloses not only the full length p75 TNFR amino acid sequence, but also the 235-residue extracellular domain (amino acids 23-257), and an N-terminal cysteine-rich fragment of this extracellular domain (162 amino acids in length) that contains the TNF-binding site. See Figure 3 at p. 1021, as well as the text at pp. 1020-1021. Smith states at p. 1021, 3rd col. that "Presumably, it is this NH_2-terminal [cysteine-rich] region that contains the TNF binding site."

In addition, the Dembic article cited by the Examiner (of which five of the seven co-authors are named inventors on the present application), published prior to the August 31, 1990 effective filing date of the present application, also makes clear that Applicants in fact had prior possession of the complete amino acid sequence of p75 TNFR. See Figure 1 at page 232 and the identification of the 235-residue TNF-binding extracellular domain at page 233, 1st col.

Dembic also reports at page 235, 1st col., the identification of a naturally occurring, N-terminally truncated soluble fragment of p75 TNFR in human urine that commences with amino acid 5 of the extracellular domain. Dembic states that "We now find that the short NH_2-terminal sequence of the second [TNF] inhibitor matches the V^5-P^9 peptide sequence of the 75-kDa TNF receptor (Fig. 1)." Because Northern blot revealed no second mRNA species that might encode this truncated version, Dembic concludes that "these TNF inhibitory peptides therefore are NH_2-terminally truncated, soluble fragments, presumably of the extracellular regions of the two TNF receptors. . . ."

Such accessible literature sources are highly relevant because, in an case analogous to the situation here, the Federal Circuit affirmed the Board's decision that the written description requirement was fulfilled even though sequences were not recited in the specification. The Court stated: "where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here 'essential genes'), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences." *Falkner et al. v. Inglis et al.* 448 F3d 1357, 1368, 79 USPQ 2d 1001 (Fed. Circ. 2006).

Moreover, the specification describes in a number of places a variety of soluble and insoluble fragments of TNFR that are capable of binding TNF (p. 7, lines 13-16), for example, proteins characterized by apparent molecular weights of 75 kD or 65 kD (p. 7, lines 19-21), and DNA sequences characterized by deletions of one or more nucleotides of FIG. 1 or FIG. 4 (p. 10, lines 1-8). The specification specifically teaches that: "On the basis of the thus-determined sequences and of the already known sequences for certain receptors, those partial sequences which code for soluble TNF-BP fragments can be determined and cut out from the complete sequence using known methods." (p. 14, lines 32-36). The specification also teaches that: "Alternatively, TNF-binding proteins may be chemically synthesized . . . . Analogues and fragments of TNF-binding proteins may be produced by the above methods. . . . These fragments and analogues may then be tested for TNF-binding activity using methods such as the assay of Example 1." (p.6, line 30 to p. 7, line 6).

Taken together with the guidance in the specification, the literature references described above demonstrate that the specification provides the requisite written description. Thus, one of ordinary skill in the art, upon reading the specification, would necessarily conclude that Applicants had possession of the full length amino acid sequence of TNFR and of numerous representative TNF-binding fragments. At least three different fragments are identified in the Smith 1990 article cited in the specification and in the Dembic publication by the inventors: the full 235-residue extracellular domain, an N-terminal 162-residue cysteine-rich fragment that contains the TNF-binding site, and a naturally occurring truncated fragment that is missing at least the first four N-terminal amino acids of the mature TNFR sequence. Construction and testing of a further number of TNF-binding fragments of TNFR is specifically contemplated in the specification, all of which demonstrates that the specification describes a sufficient number of representative species to support the genus of TNF-binding soluble fragments of TNFR fused to the hinge region of a human IgG heavy chain.

Applicants also discussed during the interview the proposed amendments to the claims. In response to Examiner Kemmerer's suggestion, Applicants have inserted the

phrase "TNF-binding" to describe the soluble fragments, to clarify that the soluble fragments as well as the complete fusion proteins are expected to bind TNF.

The phrasing of the claims as amended is thus analogous to the familiar language "polypeptide comprising a ligand-binding fragment of SEQ ID NO: X that retains ligand-binding activity". However, in Applicants' claims, "SEQ ID NO: X" is not identified by reference to an actual sequence provided in the specification but rather by reference to unique identifying characteristics of the human p75 TNFR amino acid sequence that was previously known in the art. As stated above, the Federal Circuit affirmed the Board's decision that recitation of a sequence known in the art is not necessary to meet the written description requirement. Falkner *et al.* v. Inglis, *id.*

As discussed during the interview, the reference to a "human" p75 TNFR sequence refers to naturally occurring human p75 TNFR amino acid sequence . Thus, the recitation in the claims of an insoluble human receptor that (i) specifically binds human TNF, (ii) has an apparent molecular weight of about 75 kilodaltons on a non-reducing SDS-polyacrylamide gel, and (iii) comprises SEQ ID NO: 10 is a recitation of sufficient structural and functional characteristics to uniquely identify naturally occurring human p75 TNFR amino acid sequence or natural allelic variants thereof.

Applicants presented evidence that shows that the N-terminal peptide SEQ ID NO: 10 is sufficient to uniquely identify human p75 TNFR. Exhibit S shows the results of a June 14, 2006 search of a Genbank database that includes all publicly available, non-redundant, human Genbank CDS translations (coding amino acid sequence). Over 3.5 million sequences were queried with SEQ ID NO: 10 using BLASTP, and all of the sequences that contained an exact match to SEQ ID NO: 10 are human p75 TNFR sequence or naturally occurring allelic variants thereof. If SEQ ID NO: 10 is able to uniquely identify the human p75 TNFR sequence as of June 14, 2006, then certainly SEQ ID NO: 10 was able to uniquely identify the human p75 TNFR sequence at Applicants' effective filing date. In addition, Applicants note that there are dependent claims that recite all of the peptide sequences that are found in the Smith 1990 TNFR sequence, which peptides collectively uniquely identify the human p75 TNF sequence.

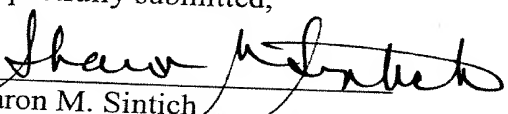
For the reasons discussed above, one of ordinary skill in the art as of Applicants' filing date, upon reading the specification, would understand that Applicants had possession of the complete p75 TNFR amino acid sequence and a representative number of TNF-binding soluble fragments. Moreover, in view of the knowledge of the complete TNFR nucleotide and amino acid sequences in the art, the claims recite sufficient identifying characteristics to meet the written description requirement. Therefore, the written description rejection should be withdrawn.

CONCLUSION

Applicants believe all pending claims are in condition for allowance. If further discussion or amendments would expedite allowance of the claims, the Examiner is asked to contact the undersigned at the number below.

Dated: October 3, 2006

Respectfully submitted,

By 

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